Synthesis of Novel Pyridazino[4,5-*b*][1,4]oxazine-3,5-diones

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Novel pyridazino[4,5-*b*][1,4]oxazine-3,5-diones were synthesized from *N*-[2-(3,4-dimethoxyphenyl)-ethyl]-2-chloroacetamide (or 2-chloropropanamide) and 1-alkyl-5-halo-4-hydroxypyridazin-6-ones in good yield.

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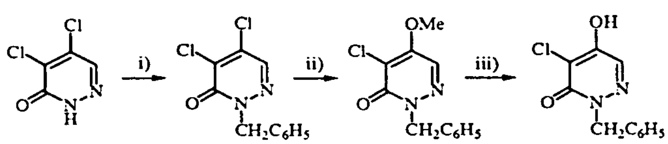
In our previous publications [1], we described the synthesis of some azeto[2,1-*a*]isoquinolin-2-ones and the pharmacological characterization of 1-(4'-methoxybenzyl)-6,7-dihydroxy-3,4-dihydroisoquinoline. In connection with our research program for the pharmacological characterization of novel isoquinoline derivatives, we attempted to synthesize some 4-[2-(3,4-dimethoxyphenyl)ethyl]pyridazino[4,5-*b*][1,4]oxazine-3,5-diones.

In this paper, we would like to report the results of the title reactions.

Compounds **4** (except for **4g**), **5** and **7** as the starting materials were prepared by Yoon's methods [1b,2]. Compound **4g** was synthesized from 4,5-dichloropyridazin-6-one *via* three steps according to Yoon's method [2] (Scheme I). The structure of **4g** was established by infrared and ^{1}H nmr spectra. The proton magnetic resonance spectrum of **4g** showed the proton signals of the hydroxy group as two broad singlet at δ 3.34 ppm for the free OH group and δ 12.21 ppm for hydrogen-bonded OH group. The area ratio of two signals is one to one, and the total integration also is for one proton.

Scheme I



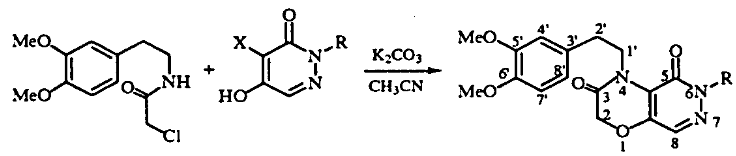
1 2 3 4g

i) Benzyl chloride, K_2CO_3, DMSO, 50-60°C.
ii) MeONa, MeOH, room temperature.
iii) 1) KOH in H_2O. 2) *conc*-HCl.

According to Konecny and his coworkers [3], the intramolecular hydrogen bond between the NH at the 5-position and the chlorine at the 4 position on the ring is influenced mainly by the character of the substituent at the N-1 position. Thus it may be considered that the intramolecular hydrogen bond of compound **4g** is similar to that of Konecny's type.

Reaction of **5** with **4** in the presence of potassium carbonate gave pyridazino[4,5-*b*][1,4]oxazine-3,5-diones **6** instead of the corresponding ethers or tertiary amines in good yields. The structures of compounds **6** were established by ir, nmr and elemental analyses.

Scheme II



5 4 6

4	a	b	c	d	e	f	g
X	Cl	Br	Br	Br	Br	Cl	Cl
R	Me	Et	Pr	*i*-Pr	Allyl	Bu	CH_2Ph

6	a	b	c	d	e	f	g
R	Me	Et	Pr	*i*-Pr	Allyl	Bu	CH_2Ph

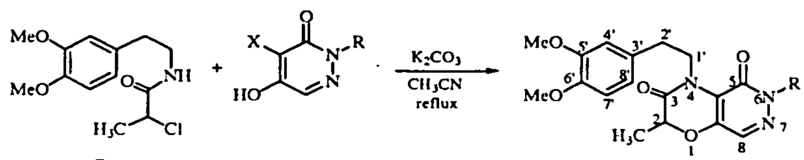
The infrared spectra of **6** showed the absorption peaks of two carbonyl bonds. However, we did not detect the absorption peaks of the NH and the OH groups. The proton nuclear magnetic resonance spectra of **6** showed proton signals for one CH_2 at the C-2 position of the oxazine ring in the δ 4.75-4.88 region as a singlet and one aromatic proton on the pyridazinone ring in the δ 7.58-8.15 region. Also we detected other proton signals such as two OCH_3, three aromatic protons, two CH_2 at C-1' and C-2' and an alkyl at the C-6 position.

The ^{13}C nmr spectra of **6** showed carbon signals for two carbonyls (δ 154.2-156.2 for C-3, δ 162.2-162.7 for C-5), one methylene for C-2 (δ 66.8-68.2) and three aromatic carbons (δ 126.8-128.4 for C-4a, δ 129.9-130.2 for C-8, δ 136.5-137.7 for C-8a) on the pyridazinooxazine ring involving the carbon signals of 3,4-dimethoxyphenyl ethyl and alkyl groups at the N-6 position.

On the other hand, cyclization of **7** with **4** afforded the corresponding 2-methylpyridazino[4,5-*b*][1,4]oxazine-3,5-diones **8** in good yield.

The infrared spectra of **8** showed the absorption peaks of two amide carbonyls in the 1690-1702 cm^{-1} range and in the 1641-1661 cm^{-1} range. The proton nuclear magnetic

Scheme III



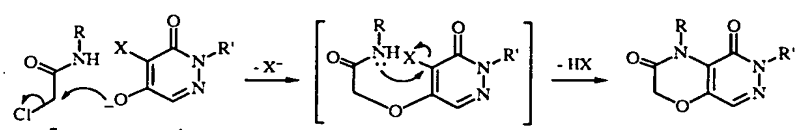
7 4 8

4	a	b	c	d	e	f	g
X	Cl	Br	Br	Br	Br	Cl	Cl
R	Me	Et	Pr	*i*-Pr	Allyl	Bu	CH_2Ph

8	a	b	c	d	e	f	g
R	Me	Et	Pr	*i*-Pr	Allyl	Bu	CH_2Ph

resonance spectra of **8** showed proton signals of one CH at the C-2 position of the oxazine ring in the δ 4.77-4.87 region as quartet, CH_3 at the C-2 position in the δ 1.42-1.63 range and one aromatic proton on the pyridazinone ring in the δ 7.54-8.08 region. We detected other proton signals such as two OCH_3, three aromatic protons, two CH_2 at C-1' and C-2' and an alkyl at C-6 position. The ^{13}C nmr spectra of **8** showed carbon signals of two carbonyls (δ 153.8-156.0 for C-3, δ 162.8-165.1 for C-5), one methyne for C-2 (δ 73.2-109.8) and three aromatic carbons (δ 126.8-128.1 for C-4a, δ 129.9-134.1 for C-8, δ 134.9-137.0 for C-8a) on the pyridazinooxazine ring involving the carbon signals for 3,4-dimethoxyphenyl ethyl and alkyl groups at the N-6 position.

Scheme IV



5 4 6

R = 3,4-dimethoxyphenylethyl- R' = alkyl-

Finally, α-chloroacetamide (for **5** and **7**) and haloenol (for **4**) moieties are good synthons for the formation of 1,4-oxazinones. The reaction mechanism is proposed in Scheme IV. Compounds **6** and **8** may be useful precursors for the synthesis of novel [6:6:6:6]-fused nitrogen heterocycles containing one pyridazine moiety.

Further work including the pharmacological characterization and other chemical transformation of pyridazino[4,5-*b*]-[1,4] oxazine-3,5-diones are under way in our laboratory.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. Open-bed column chromatography was carried out silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

1-Benzyl-4,5-dichloropyridazin-6-one (**2**).

A mixture of 4,5-dichloropyridazin-6-one (**1**, 61 mmoles, 10 g), benzyl chloride (62 mmoles, 7.8 g), potassium carbonate (66 mmoles, 9 g) and dimethyl sulfoxide (50 ml) was stirred for 7 hours at 50-60°. After cooling, the reaction mixture was filtered and washed with chloroform (100 ml). Adding chloroform (100 ml) and water (200 ml) to the combined filtrate, the solution was stirred for 10 minutes at room temperature. The organic layer was separated with a separatory funnel and evaporated under reduced pressure. The residue was applied to the top of an open-*bed* silica gel column (10 x 3 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The resulting powder was recrystallized from *n*-hexane/diethyl ether (2:1, v/v) to give compound **2** in 92% (14 g) yield.

1-Benzyl-5-chloro-4-methoxypyridazin-6-one (**3**).

A solution of **2** (41.5 mmoles, 10 g), sodium methoxide (46.3 mmoles, 2.5 g) and dry methanol (80 ml) was stirred for 10 hours at room temperature. The reaction mixture was filtered and then washed with chloroform (50 ml x 2). The combined filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-*bed* silica gel column (3.5 x 8 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The crude product was recrystallized from *n*-hexane/diethyl ether (1:1, v/v) to give compound **3** as white crystal in 94% (9.8 g) yield.

1-Benzyl-5-chloro-4-hydroxypyridazin-6-one (**4g**).

A mixture of compound **3** (40 mmoles, 10 g), potassium hydroxide (48 mmoles, 2.7 g) and water (70 ml) was refluxed for

Table 1

Yields, Melting Points and Infrared Spectral Data of Compounds **2**, **3**, **4g**, **6** and **8**

Compound No.	Isolated Yield (%)	mp (°C) (lit mp) [a]	ir (KBr, cm^{-1})
2	92	88-89 (87-89) [4]	3050, 3082, 2997, 1646, 1577, 1418, 1495, 1286, 1222, 1120, 969
3	94	99-100	3004, 2956, 1650, 1600, 1458, 1405, 1315, 1205, 1171, 1097, 942, 873, 736, 699, 650, 517
4g	96	241-242	3450, 3050, 2960, 2890, 2655, 1646, 1580, 1390, 1177, 1080, 871, 745, 697, 518
6a	77	150-151	3126, 3050, 2984, 2874, 1722, 1660, 1626, 1534, 1444, 1340, 1280, 1248, 1198, 1176, 1158, 1038, 904, 820, 776
6b	70	126-127	3082, 3026, 2964, 2848, 1710, 1650, 1620, 1522, 1428, 1384, 1342, 1262, 1238, 1174, 1140, 1024, 906, 852, 820, 760
6c	87	147-148	3078, 2962, 2958, 2870, 1712, 1650, 1620, 1522, 1424, 1384, 1340, 1264, 1238, 1176, 1140, 1024, 940, 852, 820, 800, 762
6d	72	162-163	3082, 3022, 2952, 2850, 1718, 1658, 1624, 1524, 1438, 1394, 1360, 1274, 1244, 1178, 1148, 1080, 1058, 1034, 938, 858, 826
6e	84	118-119	3082, 3004, 2954, 2872, 1714, 1650, 1624, 1520, 1464, 1624, 1384, 1340, 1262, 1238, 1158, 1140, 1050, 1022, 850, 820, 804
6f	77	104-105	3102, 3028, 2962, 2852, 1708, 1660, 1626, 1524, 1440, 1350, 1278, 1244, 1190, 1148, 1040, 1004, 950, 860
6g	89	161-163	3084, 2999, 2935, 1694, 1643, 1617, 1512, 1422, 1386, 1340, 1235, 1139, 1026, 756, 700
8a	72	134-136	2942, 1694, 1661, 1622, 1517, 1463, 1426, 1399, 1371, 1319, 1262, 1237, 1145, 1022, 803
8b	79	114-115	2937, 1693, 1660, 1613, 1515, 1422, 1379, 1262, 1028
8c	89	104-105	3100, 2980, 2900, 1715, 1640, 1535, 1435, 1400, 1280, 1255, 1040, 820
8d	84	117-118	2986, 2935, 1702, 1641, 1613, 1515, 1426, 1379, 1308, 1262, 1181, 1030
8e	81	90-91	2999, 2938, 2832, 1696, 1644, 1617, 1514, 1424, 1378, 1306, 1262, 1238, 1183, 1158, 1030, 803
8f	80	100-101	3077, 2936, 2861, 1694, 1651, 1618, 1519, 1418, 1384, 1315, 1241, 1160, 1029, 805
8g	83	135-137	2996, 2938, 2833, 1690, 1642, 1619, 1514, 1422, 1380, 1310, 1263, 1236, 1178, 1143, 1102, 1028, 755, 705

[a] Recrystallization solvents: Diethyl ether/*n*-hexane (1:1, v/v) for **3** and **6a**, diethyl ether/*n*-hexane (2:1, v/v) for **2**, methanol for **4g**; diethyl ether/chloroform (5:1, v/v) for **6b**, **6c** and **6d** and ethyl acetate for **6e**; Diethyl ether/ethyl acetate (3:1, v/v) for **6f**, ethyl acetate for **6g**, diethyl ether for **8a** and **8d**, diethyl ether/ethyl acetate (10:1, v/v) for **8b** and **8e**, chloroform/*n*-hexane (1:3, v/v) for **8c**, diethyl ether/ethyl acetate (20:1, v/v) for **8g** and diethyl ether/*n*-hexane (1:1, v/v) for **8f**.

Table 2

^1H NMR Spectral Data of Compounds **2**, **3**, **4g**, **6** and **8**

Compound No.	Solvent [b]	^1H nmr (ppm) [a] 1' CH_2 (t)	2' CH_2 (t)	5'/6' OMe (s)	4',7',8 Ar-H (m)	2 CH_2 (s)	6 CH_2 (s)	8 Ar-H (s)	Others
2	C	—	—	—	—	—	5.34 (s)	7.79	7.04 (m, Ar. 5H)
3	C	—	—	—	—	—	5.36 (s)	7.82	4.05 (s, OCH_3), 7.33 (m, Ar. 5H)
4g	D	—	—	—	—	—	5.23 (s)	7.83	3.34 (bs, 1/2 OH), 7.29 (m, Ar. 5H), 12.21 (bs, 1/2 OH)
6a	C	4.06	2.89	3.86 3.87	6.76	4.75	3.79 (s)	7.58	
6b	D	4.15	2.84	3.79 3.81	6.88	4.86	4.16 (q)	8.15	1.32 (t, CH_3)
6c	D	4.08	2.87	3.78 3.81	6.87	4.87	4.18 (t)	8.13	0.94 (t, CH_3), 1.77 (m, CH_2)
6d	C	4.07	2.90	3.85 3.87	6.76	4.76	5.33 (m)	7.66	1.34 (d, CH_3, J = 6.6)
6e	D	4.18	2.87	3.78 3.81	6.88	4.88	4.73 (m)	8.13	4.94 (m, =CH_2), 5.99 (m, CH)
6f	C	4.07	2.90	3.86 3.87	6.78	4.76	4.16 (t)	7.58	0.96 (t, CH_3), 1.37 (m, CH_2), 1.77 (m, CH_2)
6g	D	4.08	2.78	3.67 3.70	6.80	4.79	5.23 (s)	8.09	7.30 (m, Ar. 5H)
8a	D	4.08	2.77	3.70 3.73	6.76	4.86	3.63 (s)	8.03	1.42 (d, CH_3, J = 6.6)
8b	C	4.09	2.91	3.87 3.88	6.77	4.80	4.21 (q)	7.58	1.38 (t, CH_3), 1.63 (d, CH_3, J = 6.8)
8c	C	4.04	2.90	3.86 3.87	6.74	4.80	4.13 (m)	7.56	0.96 (t, CH_3), 1.63 (d, CH_3, J = 6.8), 1.82 (m, CH_2)

Table 2 (continued)

Compound	Solvent	1'	2'	^{1}H nmr (ppm) [a] 5'/6'	4',7',8	2	6	8	Others
No.	[b]	CH_2 (t)	CH_2 (t)	OMe (s)	Ar-H (m)	CH_2 (s)	CH_2 (s)	Ar-H (s)	
8d	D	4.07	2.77	3.68 3.71	6.77	4.85	5.11 (m)	8.08	1.24 (d, 2CH_3, J = 6.6), 1.43 (d, CH3, J = 6.6)
8e	D	4.09	2.78	3.69 3.72	6.76	4.87	4.64 (m)	8.05	1.44 (d, CH_3, J = 6.9), 5.18 (m, CH_2), 5.90 (m, CH)
8f	C	4.07	2.91	3.87 3.88	6.77	4.80	4.17 (q)	7.57	0.97 (t, CH_3), 1.38 (m, 2H), 1.63 (d, CH_3, J = 6.8), 1.78 (m, CH_2)
8g	C	4.05	2.88	3.85 3.85	6.76	4.78	5.32 (q)	7.59 (s)	1.62 (d, CH_3, J = 6.2), 7.37 (m, Ar. 5H)

[a] Abbreviations used: Ar = Aromatic, bs = broad singlet, s = singlet, d = doublet, m = multiplet, q = quartet, J = Hz unit. The proton signals of OH were exchangeable with deuterium oxide. Assignments of two CH_2 at C-1' and N-6 positions were proved by cosy spectra. [b] C = Deuteriochloroform, D = dimethyl-d_6 sulfoxide. [a] Abbreviations used: Ar= Aromatic, bs= broad singlet, s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. Assignments of two CH_2 at C-1' and N-6 positions were proved by cosy spectra. J = Hz unit. [b] C=Deuteriochloroform, D = dimethyl-d_6 sulfoxide.

Table 3

^{13}C Nmr Spectral Data of Compound **6**

Compound No.	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**
Solvent [a]	C	D	D	C	D	C	D
C2	68.1	66.9	66.9	68.1	66.9	68.2	66.8
C3 (C=O)	156.2	154.2	154.5	155.7	154.3	155.9	154.5
C5 (C=O)	162.4	162.4	162.4	162.7	162.4	162.5	162.2
C1'	43.5	45.9	52.1	50.2	52.9	52.4	53.8
C2'	40.7	41.9	41.9	43.5	41.9	43.5	41.8
C5'	149.8	148.6	148.6	149.8	148.6	149.6	148.7
C6'	148.8	147.5	147.5	148.8	147.5	148.7	147.6
5' OMe	56.5	55.4	55.4	56.6	55.4	56.9	55.4
6' OMe	56.6	55.5	55.4	56.6	55.4	56.9	55.6
C4a [b]	127.0	128.2	128.0	127.0	128.4	126.8	127.4
C8a [b]	137.6	136.5	136.4	137.3	136.5	137.7	136.5
C8 [b]	129.9	130.1	130.1	130.0	130.1	130.1	130.2
C3' [b]	125.9	125.5	125.4	125.3	125.5	125.6	125.4
C4' [b]	112.5	112.8	112.8	112.5	112.8	112.7	113.6
C7' [b]	112.1	111.7	111.7	112.0	111.7	112.0	112.2
C8' [b]	121.5	120.9	120.9	121.2	120.9	121.4	120.9
C-N6	34.3	33.0	33.0	34.4	33.0	34.4	32.8
Others		13.4	21.3 10.9	21.6	132.5 117.5	31.1 20.5 14.4	127.7 128.2 128.3 136.5

[a] D = dimethyl-d_6 sulfoxide, C = Deuteriochloroform. [b] Assignments may be interchanged.

Table 4

^{13}C Nmr Spectral Data of Compound **8**

Compound No.	**8a**	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**
Solvent [a]	D	C	C	D	C	C	C
CH_3-C2	16.1	17.1	17.1	16.1	16.0	17.1	15.0
C2	73.3	74.9	74.8	73.2	73.3	74.8	109.8
C3 (C=O)	154.8	155.8	156.0	154.1	154.3	156.0	153.8
C5 (C=O)	164.4	165.1	165.1	164.5	164.4	165.1	162.8
C1'	42.2	47.4	53.7	48.4	52.7	51.9	72.7
C2'	34.6	43.7	43.6	42.2	42.2	43.6	41.5
C5'	148.7	149.7	149.6	148.7	148.7	149.6	147.5
C6'	147.6	148.7	148.6	147.6	147.6	148.6	146.5
5' OMe	55.6	56.4	56.3	55.5	55.6	56.3	54.2
6' OMe	55.4	56.4	56.3	55.4	55.4	56.3	53.2
C4a [b]	127.7	127.0	126.8	127.7	128.1	126.7	127.7
C8a [b]	135.7	137.0	136.8	135.3	135.7	136.8	134.9
C8 [b]	130.2	130.0	129.9	130.1	130.1	129.9	134.1
C3' [b]	125.8	125.8	125.7	125.3	125.8	125.7	125.1
C4' [b]	113.1	112.4	112.4	113.1	113.1	112.4	119.1
C7' [b]	112.2	111.9	111.9	112.1	112.1	111.9	110.2
C8' [b]	120.9	121.3	121.3	120.9	120.9	121.3	123.7
C-N6	32.8	34.2	34.2	32.9	32.8	34.2	32.0
Others		13.9	11.4 22.1	20.5	117.4 132.3	14.1 22.2 30.8	

[a] C = Deuteriochloroform. D = dimethyl-d_6 sulfoxide. [b] Assignments may be interchanged.

3 hours. After cooling to room temperature, concentrated hydrochloric acid (10 ml) was added slowly to the reaction mixture with stirring. The product was filtered, washed with water (100 ml) and dried in air to give compound **4g**. The crude product was recrystallized from methanol to afford **4g** as white crystal in 96% (9 g) yield.

6-Alkyl-4-[2-(3,4-dimethoxyphenyl)ethyl]-2*H*-pyridazino[4,5-*b*]-[1,4]oxazine-3,5-diones **6**.

General Procedure.

A mixture of **5** (19.4 mmoles), **4** (20 mmoles), anhydrous potassium carbonate (22 mmoles) and acetonitrile (80 ml) was refluxed for 40 hours (72 hours for **4g**). After evaporating the solvent, the residue was dissolved in chloroform (50 ml). The solution was filtered and evaporated under reduced pressure. The resulting residue was applied to the top of an open-*bed* silica gel column (12 x 3 cm). The column was eluted with diethyl ether/chloroform (5:1, v/v). Fractions involving the product were combined and evaporated under reduced pressure. The crude product was recrystallized to give **6** as white crystals in good yield.

6-Alkyl-2-methyl-4-[2-(3,4-dimethoxyphenyl)ethyl]-2*H*-pyridazino[4,5-*b*][1,4]oxazine-3,5-diones (**8**).

General Procedure.

A mixture of **7** (11 mmoles), **4** (11.1 mmoles), anhydrous potassium carbonate (23.9 mmoles) and acetonitrile (50 ml, dimethyl sulfoxide for **4g**) was refluxed for 60-70 hours (8 hours for **4g**). After

Table 5

Elemental Analytical Data of Compounds **2**, **3**, **4g**, **6** and **8**

Compound No.	Molecular Formula	Analysis(%) Calcd/Found C	H	N
2	$C_{11}H_8N_2OCl_2$	51.79	3.16	10.98
		51.80	3.42	11.01
3	$C_{12}H_{11}N_2O_2Cl$	57.50	4.42	11.17
		57.80	4.65	11.35
4g	$C_{11}H_9N_2O_2Cl$	55.83	3.83	11.84
		55.98	3.97	11.90
6a	$C_{17}H_{19}N_3O_5$	59.12	5.55	12.17
		59.33	5.78	12.42
6b	$C_{18}H_{21}N_3O_5$	60.16	5.89	11.69
		60.10	6.00	11.95
6c	$C_{19}H_{23}N_3O_5$	61.12	6.21	11.25
		61.44	6.34	11.53
6d	$C_{19}H_{23}N_3O_5$	61.12	6.21	11.25
		61.36	6.40	11.32
6e	$C_{19}H_{21}N_3O_5$	61.45	5.70	11.31
		61.46	5.82	11.43
6f	$C_{20}H_{25}N_3O_5$	62.00	6.50	10.85
		61.98	6.55	10.98
6g	$C_{23}H_{23}N_3O_5$	65.55	5.50	9.97
		65.77	5.67	10.05
8a	$C_{18}H_{21}N_3O_5$	60.16	5.89	11.69
		60.04	6.03	11.47
8b	$C_{19}H_{23}N_3O_5$	61.12	6.21	11.25
		61.13	6.57	11.47
8c	$C_{20}H_{25}N_3O_5$	62.00	6.50	10.85
		61.99	6.66	11.10
8d	$C_{20}H_{25}N_3O_5$	62.00	6.50	10.85
		61.89	6.75	11.03
8e	$C_{20}H_{23}N_3O_5$	62.33	6.01	10.90
		62.37	6.21	10.89

Table 5 (continued)

Compound No.	Molecular Formula	Analysis(%) Calcd/Found C	H	N
8f	$C_{21}H_{27}N_3O_5$	62.83	6.78	10.47
		62.85	7.03	10.52
8g	$C_{24}H_{25}N_3O_5$	66.19	5.79	9.65
		66.26	6.04	9.60

cooling to room temperature, the mixture was filtered, washed with chloroform (30 ml x 2) and evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (8 x 2.5 cm). The column was eluted with ethyl acetate/chloroform (1:1, v/v for **8a**, **8c**, **8d** and **8e**; 1:2, v/v for **8b**) or ethyl acetate (for **8f** and **8g**). Fractions involving the product were combined and evaporated under reduced pressure. The crude product was recrystallized to give **8** as white crystal in good yield.

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